PB88-180260

Health Effects Assessment for Ethyl Ether

(U.S.) Environmental Protection Agency
Cincinnati, OH

May 87

U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-180260
EPA/600/8-88/039
May, 1987

HEALTH EFFECTS ASSESSMENT FOR ETHYL ETHER

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA (Please read Instructions on the reverse before completing)		
1. REPORT NO. EPA/600/8-88/039	2.	3. RECIPIENT'S ACCESSION NO. PB88 180260/AS
4. TITLE AND SUBTITLE Health Effects Assessment for Ethyl Ether		5. REPORT DATE May 1987
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		

16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 31
	20. SECURITY CLASS (This page) Unclassified	22. PRICE A02/A06

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with ethyl ether. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

> U.S. EPA. 1986b. Integrated Risk Information System (IRIS). Reference dose (RfD) for oral exposure for ethyl ether. Online. (Verification date 6/11/86, final approval pending). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities and the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Ethyl ether has not been adequately assessed for carcinogenicity, chronic toxicity or teratogenicity. A recent 90-day oral toxicity study (American Biogenics Corp., 1986) with rats showed daily doses of 2000 and 3500 mg/kg to be associated with accelerated rates of mortality; whereas, 500 mg/kg/day was a NOAEL. From these data, an RfD_{SO} of 350 mg/day and an RfD_O of 35 mg/day for a 70 kg human, were derived. A CS of 10 was calculated for mortality observed in rats at 2000 mg/day in the same study (American Biogenics Corp., 1986).

Inhalation exposure data at a single concentration suggested treatment-related changes in relative organ weights in rats and guinea pigs, but the data were inadequate for derivation of an RfD_{SI} or RfD_I. For information only, an RfD_I of 854 mg/day could be calculated from the ACGIH (1986) TLV of 400 ppm (~1200 mg/m³). This value may be adopted as the RfD_{SI} as well. These values are not recommended because the basis for the TLV is very weak.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and John Helms (Office of Toxic Substances) was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

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Office of Toxic Substances
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LIST OF ABBREVIATIONS

CS	Composite score
FEL	Frank-effect level
K_{oc}	Soil sorption coefficient
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure level
TLV	Threshold-limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected physical and chemical properties and environmental fate of ethyl ether are listed in Table 1-1.

In the atmosphere, ethyl ether is expected to exist primarily in the vapor phase. The atmospheric half-life listed in Table 1-1 is based on experimentally determined rate constants ranging from 8.9×10^{-12} to 9.3×10^{-12} cm^3 $molecule^{-1}$ sec^{-1} for the reaction of ethyl ether with HO radical at 25°C and an ambient HO radical concentration of 8.0×10^5 molecules cm^{-3} (Atkinson et al., 1979; Graedel, 1978). In aquatic systems, it appears that volatilization would be an important removal process; ethyl ether is reported to volatilize very rapidly from the surface layer of dilute aqueous solutions (Pemberton and Counsell, 1978). Using the method of Lyman et al. (1982) and an estimated Henry's Law constant of 1.26×10^{-3} atm-m^3/mol at 25°C (Hine and Mookerjee, 1975), the volatilization half-life from water 1 m deep has been calculated to be ~6 hours.

Based on its K_{oc}, ethyl ether is not expected to be significantly removed and transported through suspended particulate matters and sediments in water. Bioaccumulation in aquatic organisms also is not expected to be significant.

The half-life of ethyl ether in soil could not be located in the available literature. Its high vapor pressure (442 mm Hg at 20°C) and rapid volatilization from aqueous solution suggest that ethyl ether should volatilize rapidly from moist and dry soil surfaces. High mobility in soil is suggested by K_{oc} values of 24-73 and detection of ethyl ether in groundwater below municipal and industrial waste landfill sites (Sabel and Clark, 1984; DeWalle and Chian, 1981).

TABLE 1-1

Selected Physical and Chemical Properties
and Environmental Fate of Ethyl Ether

Property	Value	Reference
CAS number:	60-29-7	
Chemical class:	aliphatic ether	
Molecular weight:	74.12	
Vapor pressure:	442 mm Hg at 20°C	Weber et al., 1981
Water solubility:	6.46×10^4 mg/ℓ at 20°C	Valvani et al., 1981
Log octanol/water partition coefficient:	0.89	Hansch and Leo, 1985
pKa:	-3.59	Kulevsky et al., 1969
Bioconcentration factor:	2.8 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	24-73 (estimated)	Lyman et al., 1982; Sabljic, 1984
Half-lives:		
Air	26-27 hours	Atkinson et al., 1985; Graedel, 1978
Water	~6 hours	Hine and Mookerjee, 1975; Lyman et al., 1982
Soil	NA	

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Pertinent data regarding the absorption of ethyl ether after oral intake could not be located in the available literature.

2.2. INHALATION

Henderson and Haggard (1943) estimated that a man of average weight would absorb a maximum of 1.25 g of ethyl ether, resulting in a blood concentration of 0.018 g/ℓ, when exposed to an atmospheric concentration of 400 ppm (1200 mg/m³). Further details, such as the duration of exposure, were not provided in the ACGIH (1986) review of this study.

Cowles et al. (1972) exposed pentobarbital-anesthesized mongrel dogs to mixtures of four anesthetic gases including 0.65% ethyl ether, by endotracheal intubation, for 100 minutes. Inspired and end-tidal gas samples were measured every 1-2 minutes. Blood samples were taken from several sites, including the femoral artery, periodically throughout the exposure. The authors found that it took 78.9 minutes for the partial pressure of ethyl ether in alveolar gas and 92.5 minutes for the partial pressure in arterial blood to reach 50% of the partial pressure in inspired air. These results indicated that the uptake of ethyl ether after inhalation exposure was relatively slow compared with the other anesthetics tested. Because the focus of this experiment was the prediction of concentrations of anesthetic gases in various tissues, additional quantitative data regarding respiratory uptake of ethyl ether were not provided.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In a preliminary draft of an American Biogenics Corp. (1986) 90-day gavage study, 30 albino rats/sex were given 0, 500, 2000 or 3500 mg/kg/day ethyl ether. Body weight and food consumption values were recorded weekly; hematologies, clinical chemistries and urinalyses were measured at an unspecified interim period, and upon study completion, organ weight measurements and gross necropsies were performed. Histopathological analyses are in progress.

During the study, 4/60 rats (2 males and 2 females) given 2000 mg/kg/day and 15/60 rats (6 males and 9 females) given 3500 mg/kg/day died. Male rats had inhibitions in body weight gain at 2000 and 3500 mg/kg/day and decreased food consumption at 3500 mg/kg/day. High-dose males had significant decreases in hemoglobin and hematocrit values, and a slight increase in red cell count. SGPT and serum cholesterol levels were significantly increased at 3500 mg/kg/day. Although the relative weights of the brain, kidneys and testes/epididymides were increased at the high dose, the significant reductions in body weight gain in this group make interpretation difficult. Females given the high dose had inhibitions in body weight gain, elevated SGOT levels and significantly increased liver-to-body weight ratios. The dose of 2000 mg/kg/day resulted in a transient increase in serum cholesterol and elevated relative liver weights in females. There were no other treatment-related effects on hematology, clinical chemistry, urinalysis parameters or organ weights at either 500 or 2000 mg/kg/day.

The investigators observed signs of light anesthesia at 2000 mg/kg/day and, especially, at 3500 mg/kg/day. Before the final sacrifice, ophthalmic examination revealed retinal atrophy in the eye of one 500 mg/kg/day female,

two 2000 mg/kg/day females and two 3500 mg/kg/day males. Necropsies of rats given the 2000 and 3500 mg/kg/day dosages revealed lung and liver discoloration, and distention and discoloration of the stomach.

3.1.2. Inhalation. Chenoweth et al. (1972) studied the effects of repetitive ethyl ether exposure on the growth, histopathological, hematological and biochemical (SGOT and SGPT) parameters of 10 rats/sex, 6 guinea pigs/sex and 2 rabbits/sex. Each species was exposed to 2000 ppm (6063 mg/m^3) ethyl ether, 7 hours/day, 5 days/week. The numbe- of exposure days was 34/44 for rats and 33/43 for guinea pigs and rabbits. Treatment had no effect on terminal body weights in rats or guinea pigs, but it significantly decreased relative heart and liver weights in rats, and increased relative testicular weights in guinea pigs. Because only two rabbits/sex were used, it was difficult to assess effects of treatment on organ weights. No other treatment-related effects were observed.

3.2. CHRONIC

3.2.1. Oral. Pertinent data regarding the chronic oral toxicity of ethyl ether could not be located in the available literature.

3.2.2. Inhalation. ACGIH (1986) reviewed the limited data available regarding inhalation exposure to ethyl ether and concluded that narcosis and general anesthesia are the primary effects, which occur at exposures to ~3.6-6.5 volume % (109-197 g/m^3). Respiratory arrest has been associated with concentrations of 7-10 volume % (212-303 g/m^3); higher concentrations are fatal. Symptoms in occupationally exposed workers include anorexia, exhaustion, headache, sleepiness, dizziness, excitation and psychic disturbances. Blood dyscrasias, particularly in women, and albuminuria are also seen. Nelson et al. (1943) reported that 200 ppm (~600 mg/m^3) was approximately the threshold of nasal irritation and that 300 ppm (~900 mg/m^3)

was an objectionable working atmosphere. Cook (1945), on the other hand, suggested that exposure should be limited to 500 ppm (~1520 mg/m³) to avoid irritation, and stated that exposure to 500-1000 ppm (~1520-3030 mg/m³) was not associated with demonstrable injury to health.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

There were no data available on the reproductive effects of ethyl ether in humans or on its teratogenicity in experimental animals. Land et al. (1981) studied the effects of acute high level inhalation exposure to ethyl ether on spermatozoa morphology. Male mice were exposed to 0.32 or 1.6 volume % (9700 or 48,500 mg/m³, respectively) ethyl ether, 4 hours/day for 5 consecutive days. Epididymal spermatozoa were examined for morphological aberrations 28 days after the last exposure day. Neither concentration had a significant effect upon the percentage of abnormal spermatozoa, compared with control values.

3.4. TOXICANT INTERACTIONS

Ethyl ether inhibits the metabolism of hexobarbital (Vermeulen et al., 1983), acetaminophen (Watkins et al., 1984), gentamicin and tobramycin (Higashi et al., 1982), aminopyrene (Hanew et al., 1984), ethanol (Hobara et al., 1985) and N-nitrosodimethylamine (Keefer et al., 1985). Watkins et al. (1984) showed that ethyl ether inhibited conjugation of acetaminophen with sulfate, glutathione and glucuronic acid, thus slowing the rate of detoxification. In most of these studies, plasma clearance of the interacting toxicant was depressed by co-administration of ethyl ether, while volumes of distribution were unchanged. Keefer et al. (1985) found, however, that clearance of N-nitrosodimethylamine was unaffected by prior treatment with ethyl ether. The small dose of N-nitrosodimethylamine used in this study, compared with the doses of toxicants used by other investigators, may account for this difference.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the potential carcinogenicity in humans after ethyl ether exposure could not be located in the available literature.

4.2. BIOASSAYS

Pertinent data regarding the carcinogenicity of ethyl ether after chronic administration in experimental animals could not be located in the available literature. The National Toxicology Program has not scheduled ethyl ether for carcinogenicity testing (NTP, 1986).

4.3. OTHER RELEVANT DATA

Inhaled ethyl ether stimulated tumor growth in mice with subcutaneously or intravenously implanted tumor cells (Frid et al., 1984). In the same study, the mitotic index of implanted tumor cells in rats was not affected by administration of an unspecified concentration of ethyl ether.

Ethyl ether did not increase the number of revertants in five strains of Salmonella typhimurium, nor did it cause mutagenicity in three Escherichia coli strains deficient in tryptophan synthesis (DeFlora et al., 1984). Results were the same with or without S-9 mix. Abe and Sasaki (1982) found that ethyl ether had no effect on the number of sister chromatid exchanges in cultured Chinese hamster ovary cells. Ma et al. (1984) reported that ethyl ether gas did not increase micronucleus formation in the plant, Tradescantia palidosa.

4.4. WEIGHT OF EVIDENCE

Because of the lack of human and experimental animal data regarding the carcinogenicity of ethyl ether, the chemical should be categorized in IARC Group 3, Cannot Be Classified, or CAG Group D, Not Classified, applying the

criteria for weight of evidence (U.S. EPA, 1986a). These categories are reserved for chemicals with inadequate evidence of animal carcinogenicity in the absence of human data.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1985) adopted a TLV-TWA of 400 ppm (~1200 mg/m^3) for an 8-hour exposure to ethyl ether, and a TLV-STEL of 500 ppm (~1500 mg/m^3). The ACGIH (1986) cited occupational data indicating that higher concentrations in man result in irritation and narcosis. The OSHA (1985) PEL is also 1200 mg/m^3.

U.S. EPA (1986b) derived an RfD for oral exposure of 0.5 mg/kg/day or 35 mg/day for a 70 kg human. In this derivation, an uncertainty factor of 1000 was applied to the low dose of 500 mg/kg/day (NOAEL) in the 90-day gavage study using rats by American Biogenics Corp. (1986).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). The only subchronic oral study available for derivation of an RfD_{SO} is the 90-day gavage study using rats by the American Biogenics Corp. (1986). The high mortality rate at 3500 mg/kg/day clearly indicates a FEL. At 2000 mg/kg/day, 4/60 rats died, and inhibitions in body weight gain, transient increases in serum cholesterol and relative hepatic weights, retinal atrophy and gross necropsy aberrations were observed. Since one rat treated with 500 mg/kg/day had retinal atrophy, but no other effects were observed in this treatment group. Histopathological examinations did not reveal any ethyl ether-related lesions; thus, the 500 mg/kg/day dose may be considered as a NOAEL. An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for the range of intraspecies sensitivity) is applied to the NOAEL of 500 mg/kg/day to attain an RfD_{SO} of 5.0 mg/kg/day, or 350 mg/day for a 70 kg human.

6.1.2. Inhalation (RfD_{SI}). The study by Chenoweth et al. (1972) suggested treatment-related effects of ethyl ether exposure on relative organ weights of rats and guinea pigs. Since the decreases in relative heart and liver weights in rats and the increased relative testicular weight in guinea pigs were not accompanied by changes in serum enzyme levels or histopathological appearance, the significance of these effects is unclear. The short duration of the Chenoweth et al. (1972) study may have been inadequate for assessment of the cumulative effects of longer-term exposure to ethyl ether. No other data were adequate for quantitative risk assessment.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). An RfD_0 of 0.5 mg/kg/day or 35 mg/day for a 70 kg human can be derived from the RfD_{SO} of 5.0 mg/kg/day calculated in Section 6.1.1., by applying an additional uncertainty factor of 10 to expand from subchronic to chronic exposure. The RfD_0 should be re-assessed when adequate chronic toxicity or reproductive toxicity data reveal the presence of adverse effects at 500 mg/kg/day. This analysis agrees with a recent U.S. EPA (1986b) analysis in which an RfD_0 of 35 mg/day was derived in an identical manner.

Table 6-1 shows the derivation of a CS for oral intake using the American Biogenics Corp. (1986) results. Although daily exposure to 500 mg/kg ethyl ether was associated with retinal atrophy, this effect was seen grossly in only one rat, and results have not yet been confirmed histologically. The daily dose of 2000 mg/kg, which resulted in the deaths of four rats, is a more suitable value for CS derivation. Division of this dose by 10 (to approximate chronic exposure), and subsequent multiplication by the cube root of the average rat body weight to the assumed human body weight (70 kg) results in a human MED of 2311 mg/day for a 70 kg man. The human MED corresponds to an RV_d of 1.0. The RV_e for increased mortality is 10, for a CS of 10.

6.2.2. Inhalation (RfD_I). The only available toxicity study regarding chronic or subchronic inhalation exposure to ethyl ether was by Chenoweth et al. (1972). Data from this study were inadequate for derivation of an RfD_I because only one level was tested and the duration of the experiment (44 days) was too short to evaluate the subchronic toxicity of ethyl ether.

TABLE 6-1

Composite Scores for Ethyl Ether

Route	Species/ Strain	Sex	Exposure Dosage	Human MED (mg/day)	RV_d	Effect	RV_e	CS	Reference
Oral	rat/ albino	M,F	2000 mg/kg/day	2311[a,b]	1.0	increased mortality	10	10.0	American Biogenics Corp., 1986
Inhalation	guinea pig/NR	M	2000 ppm (~6060 mg/m³), 7 hours/ day, 33 days/43 days, (converted to 652 mg/kg/day[c])	977[b]	1.0	increased relative testicular weight	4	4.0	Chenoweth et al., 1972

[a]Average rat weight was ~31.5 g, from data provided by authors.

[b]Application of uncertainty factor of 10 for approximation to chronic exposure.

[c]Mean terminal body weight (as provided by authors) of 0.687 kg, and calculated daily inhalation rate of 0.33 m³ from the formula $(0.98\ W^{0.9})/2.11$, where W = body weight in kg.

NR = Not reported

The ACGIH (1986) TLV of 400 ppm (~1200 mg/m³) may be considered as a basis for an RfD_I. The TLV of 400 ppm appears to be based primarily on the data of Cook (1945), who stated that exposures to 500-1000 ppm (~1520-3030 mg/m³) did not result in demonstrable injury to health and recommended that exposures should be limited to 500 ppm to avoid irritation. Nelson et al. (1943), however, reported that 200 ppm (~600 mg/m³) was a threshold for nasal irritation and that 300 ppm (~900 mg/m³) was objectionable in the workplace. The TLV of 400 ppm, therefore, is intended to protect against irritation, narcosis and demonstrable injury to health. In derivation of an RfD_I for ethyl ether, a transformed dose of 122 mg/kg/day is calculated by expanding to continuous exposure and assuming that humans weigh 70 kg and inhale 10 m³ of air during the workday. Application of an uncertainty factor of 10 results in an RfD_{SI} of 12.2 mg/kg/day, or 854 mg/day for a 70 kg human. Because of the weak basis for the TLV, this RfD_I is not recommended, and it is suggested that a subchronic inhalation experiment of at least 90 days duration with multiple species and multiple exposure levels be performed.

The Chenoweth et al. (1972) results can be used in the derivation of a CS. Inhalation of 2000 ppm (~6060 mg/m³) ethyl ether, 7 hours/day for 33-34 exposure days resulted in decreased relative weights of the hearts and livers of rats and increased testicular weights in male guinea pigs. Chenoweth et al. (1972) stated that the mean terminal body weight of the exposed guinea pigs was 687 g. Assuming a guinea pig of this weight inhales 0.33 m³ of air/day [using the formula of U.S. EPA (1986c)], and converting to continuous exposure, the air concentration of 6060 mg/m³ is equivalent to a dose of 652 mg/kg/day. Division of this equivalent dose by 10 (to approximate chronic exposure), and multiplication by the cube root of the

ratio of animal to human body weights results in a human MED of 977 mg/day for a 70 kg human. This MED corresponds to an RV_d of 1.0. When the RV_d is multiplied by an RV_e of 4 (for changes in organ weights), the resulting CS is 4.0 (see Table 6-1).

6.3. CARCINOGENIC POTENCY (q_1^*)

Because of the lack of carcinogenicity data for ethyl ether, determination of carcinogenic potency is not possible.

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APPENDIX

Summary Table for Ethyl Ether

	Species	Experimental Dose	Effect	Reference Dose (mg/day) or CS	Reference
Oral					
RfD_{SO} (formerly AIS)	rat	500 mg/kg/day for 90 consecutive days (NOAEL)	retinal atrophy in one rat	350	American Biogenics Corp., 1986
RfD_{O} (formerly AIC)	rat	500 mg/kg/day for 90 consecutive days (NOAEL)	retinal atrophy in one rat	35	American Biogenics Corp., 1986; U.S. EPA, 1986
Maximum					
CS	rat	2000 mg/kg/day for 90 consecutive days (oral)	increased mortality	CS=10.0	American Biogenics Corp., 1986; U.S. EPA, 1986